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Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring

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ABSTRACT

Ictal-related cardiac asystole is supposed to be a risk factor for *sudden unexpected death in epilepsy* (SUDEP). We retrospectively analyzed the occurrence of ictal asystole in 2003 epilepsy patients undergoing long-term video EEG/ECG monitoring from 1/1999 to 6/2010 at the Freiburg epilepsy centre. Seven patients had cardiac arrest with a duration of at least 3 s; 6 ictal, one postictal. In all patients, the temporal lobe was involved in ictal activity based on neurophysiological investigations or morphological lesion. Whereas asystole was self-limited in six cases, one patient with insular seizure origin had to undergo cardiopulmonary resuscitation. Interestingly, also patients with a short history of epilepsy, low seizure frequency and under treatment in monotherapy showed episodes of asystole. In all cases, even with brief cardiac arrest, asystole was associated with subsequent EEG flattening.

In conclusion, ictal asystole is a rare event even in a population undergoing major changes in antiepileptic medication. Temporal lobe epilepsy was associated with a risk for asystole; cardiac arrest also occurred in patients who, based on their history, might have not been considered at elevated risk for SUDEP.

1. Introduction

The mean incidence of *sudden unexpected death in epilepsy* (SUDEP), as one of the risk factors of a premature mortality in epilepsy patients, is on average about 1.8/1000.[1,2] It is elevated particularly in patients with refractory epilepsy.[3] The underlying pathophysiology is not completely understood but seizure-related pulmonary oedema, central apnoe, and neurogenic cardiac asystole are discussed as contributing to SUDEP.[4]

A prevailing hypothesis is that SUDEP is caused by seizure-induced cardiorespiratory disturbances, mediated by the autonomic nervous system, with a direct effect on the heart as a consequence of an imbalance between parasympathetic and sympathetic activity.[5] Seizure-related tachycardia in temporal lobe epilepsy occurs frequently without clinical consequences,[6,7] whereas seizure-related asystole and bradycardia are much less common.[8,9] Ictal bradycardia and asystole have been implicated as a cardiac cause of SUDEP.[10] Many brain stimulation studies documented the cortical influence on cardiovascular responses like heart rate,[11] and a number of case reports suggest their clinical relevance.[12,13]

We here analyzed the incidence of ictal cardiac arrest and clinical characteristics of patients affected in a large patient cohort.

2. Methods

We retrospectively analyzed the files of patients with medically refractory epilepsy who underwent presurgical or diagnostic video EEG monitoring between 1999 and 2010 in the Freiburg epilepsy centre. In each patient, medical history was taken and a neurological examination was performed before long-term monitoring was started. Additionally, the diagnostic protocol included a comprehensive neuropsychological test battery and high-resolution brain *magnetic resonance imaging* (MRI; Fig. 1). EEG recordings were performed using surface electrodes placed according to the international 10–20 system with, when necessary, additional sphenoidal electrodes and 10–10 electrodes as well as EOG and ECG coregistration. Invasive electrodes like subdural grids and strips or depth electrodes were placed individually according to the hypothesis about the seizure onset zone. EEG data during video-EEG-monitoring were acquired using video-EEG-systems from IT-med (Usingen, Germany), or Compumedics (Abbotsford, Australia). During monitoring, antiepileptic drugs were partially or totally withdrawn. Video and electrophysiological data from continuous video EEG/ECG monitoring were analyzed in terms of semiological phenomena and seizure patterns including region and lateralization of seizure onset and spread. ECG was analyzed

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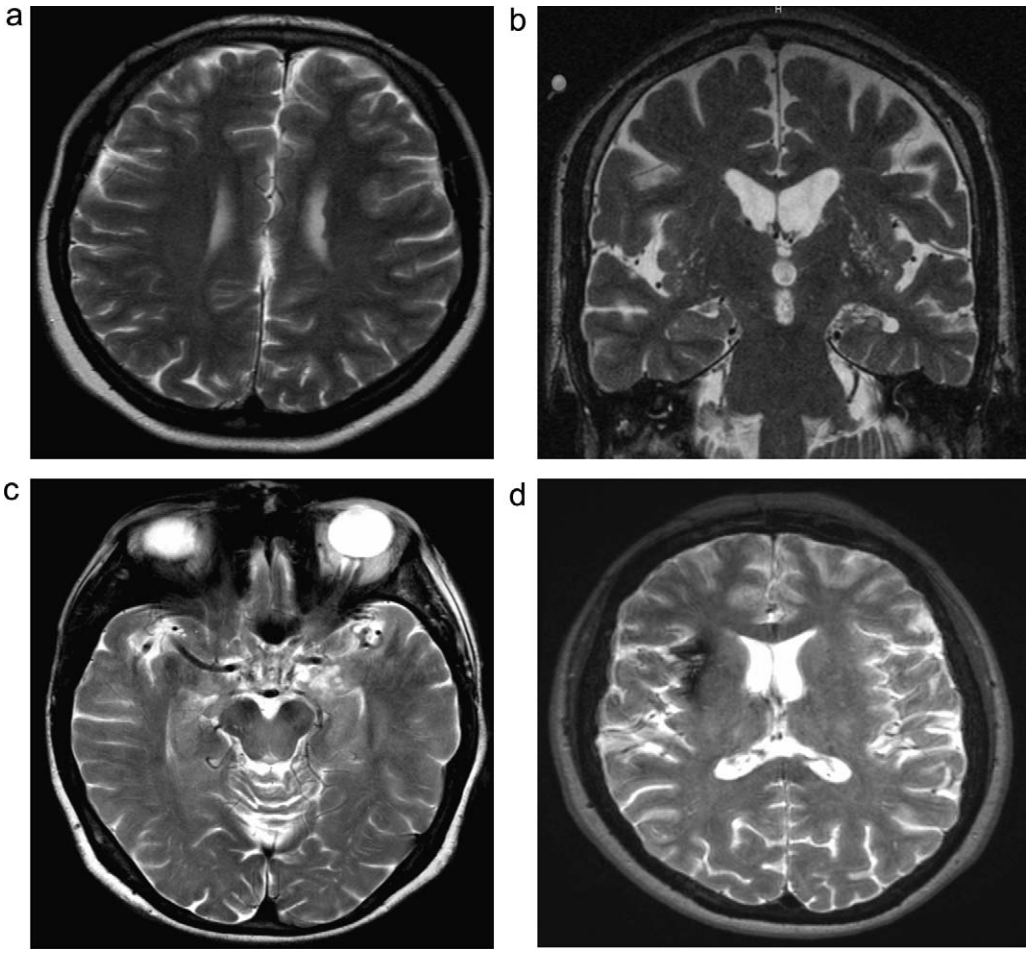

Fig. 1. MR imaging of the four lesional cases. (a) Multiple subependymal paraventricular heterotopic nodules left ventricle. (b) Hippocampal sklerosis left. (c) DNET left temporal. (d) Cavernoma insular right.

for bradycardia, tachycardia, arrhythmia, disturbances of conductions, and asystoles. Classification of epilepsy syndromes and seizure types was performed according to the criteria of the international league against epilepsy.[14] For inclusion into this study, a minimum continuous monitoring period of 24 h was required to be regarded as long-term monitoring.

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

3. Results

2003 patients underwent long-term video-EEG-monitoring in the years from 1999 to 2010 in Freiburg (1217 for presurgical evaluation, 786 for syndromatic classification and therapy monitoring). This corresponds to a total of 9534 monitored patient days.

7 patients (0.34%; 5 female and 2 male, mean age 45.8 years (range 27–65 years)) suffered an ictal or in one case postictal (patient 7) asystole during video-EEG-monitoring. Mean onset of epilepsy was at the age of 25.4 years (range 7–65 years), the mean duration of epilepsy was 16.4 years (range 1–35 years).

Asystoly occurred early in the course of epilepsy in 2/7 patients (12 months and 14 months after initial clinical manifestation, respectively, Table 1).

Syndromatically, all patients suffered from focal epilepsy. Table 2 summarizes the type of epilepsy, the etiology, seizure types and frequencies, MRI-based localisation of the lesion, EEG findings and antiepileptic medication. In four out of seven patients, MRI scans showed lesions (limited to the temporal lobe in patients 4 and 5, including the temporal lobe but also other regions in patient 1, located in the right insula in patient 6). Three patients remained cryptogenic despite the use of dedicated MR protocols including high-resolution imaging of the temporal region.

EEG recordings obtained during seizures associated with asystole gave evidence of left temporal seizure onset in two cases and right temporal seizure onset in three cases. In two cases, early bilateral activity was recorded, with temporal predominance in one case (patient 5) and widespread EEG changes in the other (patient 1). At the time of asystole, however, ictal EEG acitivity had spread considerably in all cases. In one patient (6) ictal activity spread from right temporal to left temporal lobe immediately prior to the occurrence of asystole. Overall, evidence for the involvement of the temporal lobe was present in all cases of our patient collective, morphologically and/or electrophysiologically.

Five out of seven patients had been unresponsive to at least two antiepileptic drug regimens. Four patients were on monotherapy before video EEG monitoring started, two were under a combination of two antiepileptic drugs and one patients was treated with four antiepileptic drugs. At the time of asystole, antiepileptic medication had been reduced in 4 out of 7 patients; in one of them AEDs had been completely tapered off (Table 2).

All cases of ictal asystole occurred during a complex partial seizure. In each case, even in the patient with an asystole lasting only 3 s, there was a flattening of electrical brain activity during the asystole, and loss of muscle tone, at times with myoclonic

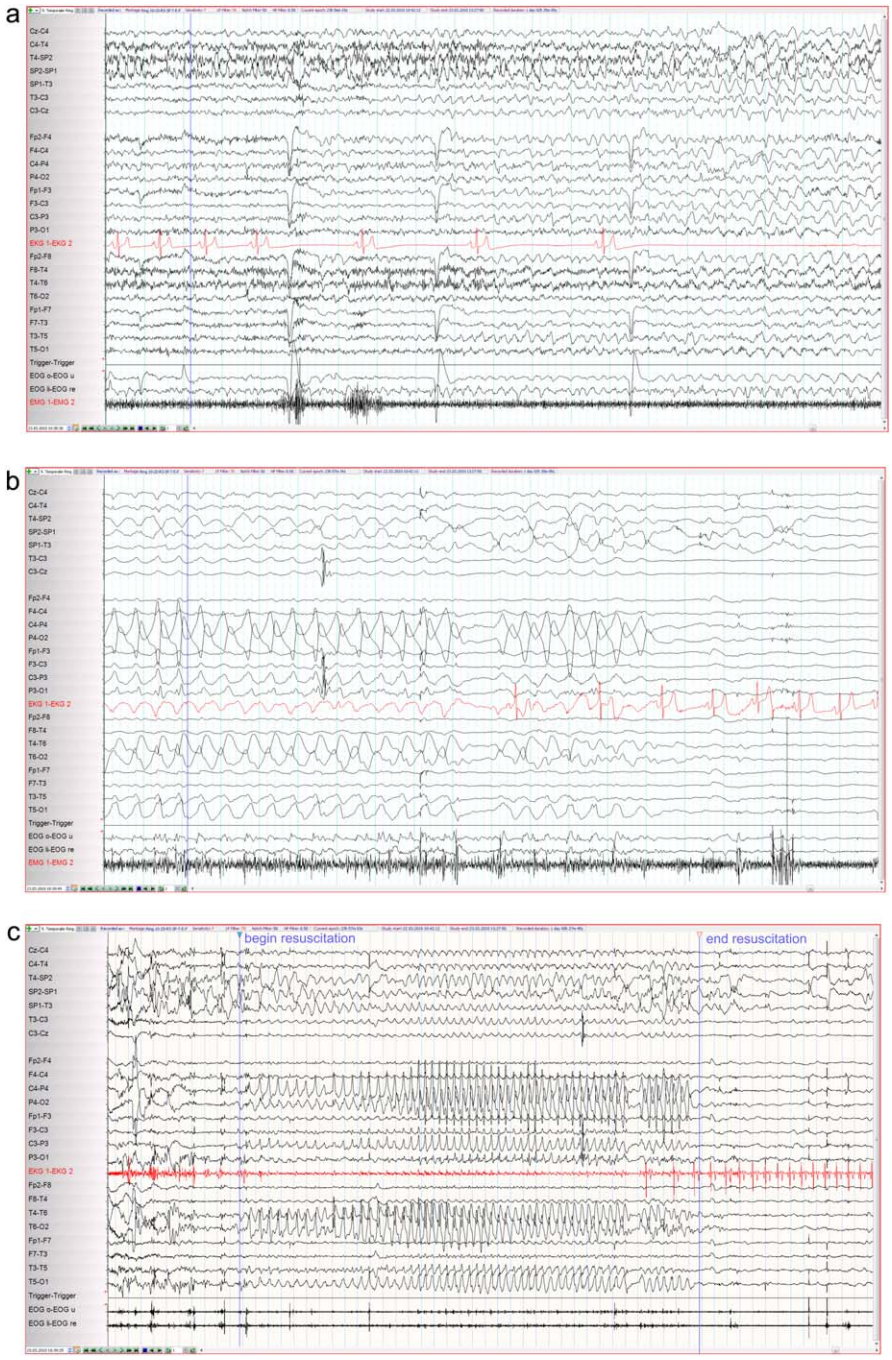

Fig. 2. Onset (a) and end (b) of asystole in patient 6. (c) Beginning and end of resuscitation.

components. In one patient (6; Fig. 2) cardiovascular resuscitation was started 44 s after the last QRS complex and was successful after 32 s of cardiac massage. At the time of cardiac arrest, the seizure lasted 37 s and EEG showed bitemporal rhythmic theta/delta activity.

In one case, bradycardia and in two cases tachyarrythmia was preceding the asystole, whereas in the other patients ECG had remained unchanged before asystole.

No patient had interictal clinically relevant cardiac symptoms; in one case a left bundle branch block was pre-existing.

Table 1
Demographic data.

	Patients						
	1	2	3	4	5	6	7
Sex	F	M	F	F	M	F	F
Age (years)	27	41	47	63	65	55	23
Age at onset of epilepsy (years)	7	40	15	62	15	19	20
Duration of epilepsy before documented ictal asystole (years)	20	1	32	1.2	23	35	3

Table 2
Neurophysiological findings, MRI and antiepileptic medication.

	Patients						
	1	2	3	4	5	6	7
Type of epilepsy Etiology	Focal, symptomatic Multiple subependymal paraventricular heterotopic nodules	Focal, cryptogenic Not known	Focal, cryptogenic Not known	Focal, symptomatic DNET	Focal, symptomatic Hippocampal sklerosis	Focal, symptomatic Cavernoma, Insulär right	Focal, cryptogenic Not known
MRI localisation	Left ventricle including temporal horn	–	–	Left temporal	Left temporal	Right insular	–
Seizure types	SPS CPS	SPS CPS SGTCS	SPS CPS SGTCS	SPS CPS	SPS CPS SGTCS	SPS CPS SGTCS	CPS SGTCS
Frequency of seizures per year	SPS: 7000 CPS: 6200	SPS: 24–84 CPS: <6 SGTCS: 2	SPS: un CPS: 120/a SGTCS: un	SPS: un CPS: 12/a	SPS: 24/a CPS: 24/a SGTCS: 24/a	SPS: no CPS: 12/a SGTCS: 1/35a	CPS: <50/a SGTCS: 1/a
EEG findings at seizure onset	Extended bilateral diffuse amplitude depression	Rhythmical 6/s theta waves temporoposterior right	Lafa temporobasal and temporolateral left	Rhythmic Delta fronto centro temporal left	Bitemporal rhythmic delta activity	Rhythmical 7/s theta activity temporoant right (SP2)	Rhythmical activity temporoant right (SP2)
AED prior to monitoring [mg]	CBZ 1200	CBZ 1600 PRI 125	VPA 900 LTG 300	TPM 1200	OXC 1800	LEV 1500 VPA 600 CLB 5 ESL 1600	LEV 3000
AED at time of asystole [mg]	CBZ 1200	CBZ 1600	LTG 300	No AED	OXC 1800	LEV 1500 ESL 800	LEV 4500 VPA 3300
Drug withdrawal	No	Yes	Yes	Yes	No	Yes	Yes

SPS: simple partial seizures; CPS complex partial seizures, SGTCS secondary generalised tonic clonic seizures; Lafa: Low amplitude high frequency activity; AED antiepileptic drug; CBZ: Carbamazepine; CLB: Clobazam; PRI: Primidone, LTG: Lamotrigine; LEV: Levetiracetam TPM: Topiramate; OXC: Oxcarbazepine; ESL: Eslicarbazepine; VPA: Valproate.

Table 3
Cardiac status.

	Patients						
	1	2	3	4	5	6	7
Interictal ECG	Normal	Normal	Singular extrasystoles	Left bundle branch block	Normal	Normal	Postictal bradycardia
Ictal ECG	AV Block III	Sinus arrest	AV Block III	AV Block III	AV Block III	Sinus arrest	Sinus arrest
Duration of asystole [s]	3 and 6	25	35	34	29	77	5
ECG before and after asytole	SR	Tachyarrythmia/ bradyarrythmia	SR	SR	SR, bradycardia	Tachyarrythmia/ bradyarryhtmia	Bradycardia/ tachycardia
Cardiovascular risk factors	No	No	Essential hypertonus	Essential hypertonus	No	No	No
Time interval between seizure onset (EEG) and onset of asystole	35 s after seizure onset	229 s after seizure onset	Un	3 s after seizure onset	20 s after seizure onset	37 s after seizure onset	24 s after seizure ending
Flattening of electrical brain activity before end of asystole	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pacemaker implantation	Yes	Yes	Yes	Yes	Yes	Yes	No/event-recorder

SR: sinus rhythm, un: unknown.

Table 3 shows characteristics of cardiac functions of the seven patients.

After ictal asystole, 6 out of 7 obtained a cardiac pacemaker; in the one patient having an postictal asystole an event recorder was implanted; follow-up is still pending. There were no cases of death during monitoring and no cases of SUDEP among the 7 patients showing ictal asystole after a mean follow up of 5.6 years.

4. Discussion

In this large cohort, cardiac asystole occurred in 7 out of 2003 patients (0.34%). This is in line with the reported 0.27–0.4% of patients suffering ictal asystole during prolonged video EEG telemetry.[15] It is of interest that the observed rate of 1 asystole in 3.7 patient years is about at least ten times higher than the incidence of SUDEP in pharmacoresistant epilepsy patients.[16] In particular, there was only one single case of SUDEP-like event requiring cardiopulmonarly resuscitation during the 10.5-year observation period and no SUDEP occurred during monitoring.

The frequency of asystole per patient year is similar to a report of a small patient group undergoing long-term ambulatory ECG monitoring.[17] The authors found an incidence of asystole of 4 in 19 patients (16%) monitored for a median period of 18 months and a total monitoring duration of 9167 patient days. It is of note that under monitoring conditions, despite frequent changes in medication, similar frequencies of asystole per patient year were found, whereas the patients monitored by Rugg-Gunn et al.[17] may be expected to have had more stable drug regimens.

MRI and EEG findings emphasise the crucial role of the temporal lobe in cardiovascular autonomic control.[5] This is consistent with reports that TLE surgery may reduce the incidence of SUDEP.[18] It has been discussed that there may be a preferential role of the left hemisphere in the genesis of ictal bradycardia,[19] and more specifically of the left temporal lobe.[12] So ictal bradycardia is seen primarily in seizures involving the temporal lobe, but may occur particularly with bilateral spread of ictal activity.[10] In this cohort, ictal asystole was about as frequent for seizures originating from the left side as for seizures starting from the right side or bilaterally. Two of the patients with right temporal seizure onset showed a relevant tachycardia preceding the asystole, possibly due to a higher sympathetic influence.[13]

Ictal asystole was not related to pre-existing cardiac disease. None of the patients had ECG recordings which would have required any type of treatment, and even long-term interictal ECG recordings did not reveal a risk of asystole.

Cardiac asystoles in our patients lasted between 3 and 77 s and all patients had a flattening of brain activity, suggesting cerebral hypoxia, which has been considered a cofactor leading to death, but we could not observed immediate onset of flat EEG which would support the hypothesis whether SUDEP is caused by "electrical shutdown of brain activity".[20] There is insufficient data available to decide if brief periods of asystole are to be considered a benign condition,[21] or if widespread consequences to cerebral blood supply may be a risk factor contributing to SUDEP-like events.

It is of interest that the clinical characteristics of the patients having asystole in this study only partially overlap with commonly assumed risk factors for developing SUDEP: only patients with focal epilepsy had an asystole, five out of seven of these patients had undergone reduction of medication,[22] and two of them were under treatment with carbamazepine.[23,24]

The fact that only patients with focal epilepsy showed ictal asystole may point to pathophysiological aspects of cardiac influences of epileptic activity, and correlates well with a shorter life expectancy of patients particularly with focal epilepsy.[25] In this cohort, asystole did not occur during generalised tonic–clonic seizures, which are considered a risk factor for SUDEP. Only four patients had a long-lasting epilepsy and five were pharmacoresistant[2,17] at the time of evaluation, whereas asystole occurred also in two patients with only 12–14 months of epilepsy duration. Four patients with asystole were under monotherapy, whereas patients under polytherapy are considered to be at higher risk for SUDEP.[26,17]

The most severe case necessitating cardiopulmonary resuscitation to prevent SUDEP had a long-lasting, parmacoresistant epilepsy, an insular structural lesion, and was under polytherapy. However, a lack of common risk factors in the patient history is not sufficient to exclude an individual risk for the occurrence of asystole.

Our data strongly suggest that not all patient suffering from asystole will develop SUDEP, although in the individual patient there are presently no criteria to predict which patients are at particular risk. Multicentric analyses such as presently envisaged in the Mortemus project[27] may contribute to a better understanding of the role of asystole in SUDEP in the future.

5. Conclusion

This retrospective monocentric analysis confirms that ictal related cardiac asystole is a rare event that occurred in seven out of 2003 patients with epilepsy in 9534 monitored patient days. Those patients had temporal lobe or insular epilepsy. A short duration of epilepsy and normal evaluation of cardiac functions do not preclude a risk of ictal asystole when experiencing complex focal

seizures with temporal involvement. Despite frequent changes in the antiepileptic drug regimen, there were no SUDEP cases during monitoring, but one patient who shared established risk factors had to undergo cardiopulmonary resuscitation to prevent the development of SUDEP.

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